

Johns Hopkins University

**SYSTEMATIC REVIEW IN VERTEBRATE ANIMAL RESEARCH:  
BEST PRACTICES FOR INSTITUTIONS OF HIGHER EDUCATION**

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## Glossary

*Administrative Burden* – Process-oriented policies that take up large amounts of time and resources, but do not directly benefit a program or initiative. Generally understood in a research setting as those processes involving a large amount of paperwork, certification, or reporting. They may be governmental or institutional.

*Animal Program* – In this context, the Animal Program refers to the institutional body tasked with oversight of all animals on a research campus. It may be comprised of the IACUC, Attending Veterinarian, Institutional Official, and other staff.

*Attending Veterinarian* – In the United States, research institutions are required to appoint a single veterinary expert, who is ultimately responsible for the care and well-being of all vertebrate animals on campus.

*Clinical Trial* – An experiment investigating the effectiveness of a device or drug in human research subjects.

*Compliance* – In a research setting, compliance with institutional policy or governmental regulation.

*IACUC* – A committee of individuals tasked with reviewing a proposed animal experiment, and approving or rejecting it based on the three principles of refinement, reduction and replacement. Many countries require some form of IACUC at their research institutions, including the United States.

*Institutional Official* – In the United States, research institutions are required to appoint a member of senior leadership that is ultimately responsible for the animal program in its entirety, including the administration of institutional policies, training, and procedures.

*Intervention* – Any treatment, medicine, or device introduced to a human being in a medical experiment to test its effect or introduced as common medical practice to treat an ailment.

*Meta-analysis* – The statistical analysis of data resulting from multiple studies. The goal of meta-analysis is to find statistical commonalities or demonstrate disparities within a group of similar or identical trials. Meta-analysis serves to test the validity of an experiment that has been repeated over time.

*Misconduct* – Commonly understood to be the promotion or publishing of false, fabricated, or deliberately misleading scientific data. Misconduct also includes the use of unethical or illegal methods, or materials as well as experiments that do not conform to governmental regulation or institutional policies.

*Preclinical Trial* – Test of a drug or device using tissue culture, computer model, animal experimentation or a combination thereof. These trials occur before a clinical trial to determine potential effects on human participants.

*Protocol* – The step by step procedure to be conducted as the “experiment.”

*Publication Bias* – The conscious or subconscious reliance on a limited body of literature. Also used to describe the failure to report negative or unfavorable research results.

*Reduction* – Determining the statistically relevant population size needed in any experiment. The goal of reduction is to reduce the number of animals used in scientific experimentation as best as practicable.

*Refinement* – Specifically tailoring an experiment by minimizing or eliminating unnecessary pain or distress to an animal subject.

*Replacement* – Substitution of non-living methods or models in place of vertebrate animals in a scientific experiment.

*Reproducibility* – When used in the sciences, reproducible results are verifiable by an independent researcher doing the same experiment.

*Scientific Merit* – An experiment is thought to be meritorious if it is ethical in conduct, advances our understanding of the universe, and makes a novel contribution to a relevant scientific discipline.

*Systematic Review* – The literature review of an entire body of work on a given topic in an effort to understand; a.) what was done before, and b.) what was proven effective (or ineffective). Systematic review helps determine if repeating or expanding an experiment is necessary.

*The Guide* – The Guide for the Care and Use of Laboratory Animals. Compliance with recommendations in the Guide is required by institutions receiving funding from the US Public Health Service (CDC, National Institutes of Health, Department of Health and Human Services).

*Translational Research* – Basic fundamental research that one day may lead to a medical treatment, device, or drug for use by human beings.

*Vertebrate* – Any land or sea creature with a spine. In many countries, vertebrate animals are afforded legal protection as subjects in scientific experiments.

## Abstract

Systematic review is the comprehensive review of an entire body of research. These reviews compare independently published results for trends such as efficacy and reproducibility. Systematic review also helps protect human subjects from harmful or otherwise ineffective treatments. Therefore, it is common practice in human subjects research to conduct a systematic review.

However, systematic review is not common in preclinical research with animals. Basic research that leads to clinical trials is known as *translational* research, and often involves preclinical research using animal subjects. Many advances in medicine can be attributed to animal experimentation. For these reasons, the scientific community has called for increased systematic review in the drafting of animal experimental protocols.

This report had three specific aims. This project examined the benefits of systematic review and underlying problems resulting from a lack of systematic review in animal protocol development. Secondly, this project explored four spheres of institutional influence. The cultural, administrative, training, and policy-related aspects of the institution were found to be problematic. This project also examined ways in which each sphere of influence might help an institution promote systematic review. Thirdly, this report provides recommendations for institutions, based on the results of the research. Recommendations fall within each of the four spheres of institutional influence.



## Abbreviations

AAMC	Association of American Medical Colleges
APHIS	United States Department of Agriculture “Animal and Plant Health Inspection Service”
AWA	Animal Welfare Act
AWR	Animal Welfare Regulations
BMJ	The British Medical Journal
CAMARADES	Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies
Cochrane	Cochrane Database of Systematic Reviews
COGR	Council on Governmental Relations
CONSORT	Consolidated Standards of Reporting Trials
ECPC	Effective Care in Pregnancy and Childbirth (Project)
FASEB	Federation of American Societies for Experimental Biology
FDA	United States Food and Drug Administration
IACUC	Institutional Animal Care and Use Committee
ICLAS	International Council for Laboratory Animal Science
IRB	Institutional Review Board (for human subjects research)
JAMA	The Journal of the American Medical Association
NABR	National Association for Biomedical Research
NC3Rs	National Centre for the Replacement, Refinement, and Reduction of Animals in Research
NCURA	The National Council of University Research Administrators
NIH	The National Institutes of Health

NLM	The National Library of Medicine
OLAW	Office of Laboratory and Animal Welfare
PHS	United States Public Health Service
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RIO	Research Integrity Officer
SRA	Society of Research Administrators, International

## Chapter 1. Introduction

### 1.1. Background

The utilization of vertebrate animals in biomedical research dates back to antiquity.<sup>1</sup> A major facet of vertebrate animal research is *translational* research. Translational research is defined as basic and preclinical research that may one-day lead to a human health intervention, or the ultimate commercialization of a device or drug.<sup>2</sup> Many advancements in human health are attributed to animal subjects research. The Nobel Prize-winning contributions of Robert Koch (1843-1910) aided in the identification of tuberculosis as a communicable disease.<sup>3</sup> By inoculating guinea pigs with tissue known to contain the bacterium, Koch demonstrated the transmittable nature of the disease.<sup>4</sup> Similarly, research on the effects and treatment of HIV in macaques has made significant progress towards a clinically viable vaccine.<sup>5</sup>

However, research on vertebrate animals is not without debate. Issues of pain and distress for the benefit of society are commonplace topics of ethical discourse. Issues of experimental design and merit dominate the scientific debate. However, ethical conduct and scientific merit are increasingly seen as interdependent.

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<sup>1</sup> Franco, Nuno Henrique. "Animal Experiments in Biomedical Research: A Historical Perspective." *Animals : an Open Access Journal from MDPI* 3, no. 1 (2013). <https://dx.doi.org/10.3390%2Fani3010238>

<sup>2</sup> Woolf, Steven H. "The Meaning of Translational Research and Why It Matters." *JAMA* 299, no. 2 (2008): 211-13. <http://dx.doi.org/10.1001/jama.2007.26>

<sup>3</sup> Blevins, Steve M. and Michael S. Bronze. "Robert Koch and the 'Golden Age' of Bacteriology." *International Journal of Infectious Diseases* 14, no. 9 (2010): e744-e51. <http://dx.doi.org/https://doi.org/10.1016/j.ijid.2009.12.003>

<sup>4</sup> Kaufmann, Stefan H. E. and Ulrich E. Schaible. "100th Anniversary of Robert Koch's Nobel Prize for the Discovery of the Tubercle Bacillus." *Trends in Microbiology* 13, no. 10 (2005): 469-75. <http://dx.doi.org/https://doi.org/10.1016/j.tim.2005.08.003>

<sup>5</sup> Van Rompay, Koen K. A. "Tackling Hiv and Aids: Contributions by Non-Human Primate Models." *Lab Animal* 46 (2017): 259. <http://dx.doi.org/10.1038/labani.1279>

In 1959, William Russell and Rex Burch authored “The Principles of Humane Experimental Technique.” Their work set the stage for a harmonized international understanding of the ethical treatment of research animals. Three principle concepts were developed, commonly known as the “3Rs.” The first principle, *replacement*, is defined as practices that replace vertebrates with machines, computing models, or non-vertebrate organisms such as “higher plants, microorganisms, and the more degenerate metazoan endoparasites.”<sup>1</sup> *Reduction*, the second principle, is more complex. In the simplest terms, reduction involves experimenting on the smallest population size possible to achieve statistically relevant results.

Lastly, is the principle of *refinement*, which is a refinement of the experimental approach. A refined method causes the minimal practicable harm to the animal. Common refinement approaches include pain management and, when necessary, euthanasia or “humane endpoints.”<sup>2</sup> These three principles are actively promoted in the United States through the implementation of animal welfare regulation.

Two regulations govern all vertebrate animal research conducted in the United States. Compliance with The Animal Welfare Act (AWA) and related Regulations (AWR) are enforced by the U.S. Department of Agriculture Animal and Plant Health Inspection Service (APHIS).<sup>3</sup> Signed into law in 1966, the Animal Welfare Act was largely intended to regulate commercial use and transport of animals in agriculture; however, these regulations also apply to all

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<sup>1</sup>Russell, William M. S. and Rex L. Burch. "The Principles of Humane Experimental Technique." (1959). <http://books.google.com/books?id=j75qAAAAMAAJ>

<sup>2</sup> NRC, National Research Council. *Guide for the Care and Use of Laboratory Animals*. Edited by National Research Council (U.S.), Committee for the Update of the Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Research (U.S.), and National Academies Press (U.S.). 8th ed. Washington, D.C.: National Academies Press, 2011. <http://www.ncbi.nlm.nih.gov/books/NBK54050>

<sup>3</sup> 89-544, P.L. *The Animal Welfare Act (Laboratory Animal Welfare Act of 1966, P.L. 89-544)*. 1966.

institutions involved in research on vertebrate animals. The law requires that research institutions form an oversight committee, commonly known as the Institutional Animal Care and Use Committee (IACUC).

The Health Research Extension Act of 1985 granted the U.S. Public Health Service (PHS) the authority to regulate the use of animals in research.<sup>1</sup> This second set of regulations is commonly referred to as the “Public Health Service Policy” and is enforced by the Office of Laboratory and Animal Welfare (OLAW). PHS regulation is applicable to all PHS-funded research involving animals. This includes all research supported by the National Institutes of Health (NIH). PHS policy also includes a mandate for an Institutional Animal Care and Use Committee.

Additionally, PHS policy requires compliance with recommendations published in the “Guide for the Care and Use of Laboratory Animals,” commonly referred to as “The Guide.”<sup>2</sup> The Guide is maintained by the National Research Council of the National Academies and is considered the gold standard for best practices promoting reduction, replacement, and refinement in vertebrate animal research. Although not a regulatory document, there is a requirement that PHS-grantee institutions must comply, making the Guide a de facto regulatory publication. The Guide addresses the responsibilities of the IACUC. IACUC oversight includes not only the approval of animal protocol, but also housing, inspections, training, and hygiene. An IACUC has two primary directives. Firstly, to protect the wellbeing of animals used in institutional research,

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<sup>1</sup> OLAW, Office of Laboratory Animal Welfare. "Public Health Service Policy on Humane Care and Use of Laboratory Animals." (Revised 2015).  
<https://grants.nih.gov/grants/olaw/references/phspol.htm#AnimalWelfareAssurance>

<sup>2</sup> NRC, National Research Council, *Guide for the Care and Use of Laboratory Animals*, 2.

and second, to comply with the law. However, many feel that the role of the IACUC is evolving, and that institutional responsibility goes beyond animal well-being and regulatory compliance.

## 1.2. Statement of the problem

Human clinical trials are designed based on systematic review, meta-analyses, or a combination thereof. The practice of systematic review goes beyond that of the literature search for prior results. A literature review is very limited in scope. It serves as a review of prior analysis or experimentation with an aim to build something new to further our knowledge of a given topic. Literature review is subject to both intentional and unintentional selective bias on behalf of the curator.<sup>1</sup> For example, during a literature review, a scientist learns that many rat calls have been identified using ultrasonic analysis, but no one knows if the calls of rats living in a laboratory environment differ from those of wild rats.<sup>2</sup> The scientist then focuses her literature search on those publications related to ultrasonic analysis of rat calls. Based on this literature review, she creates an experiment to examine rat calls in the wild. This type of literature search helps create new experiments that build on an existing experimental approach, and represents a fundamental aspect of the scientific method.

However, a *systematic* review is a comprehensive review of many datasets is an effort to more broadly capture a field of inquiry. For example, a scientist wishing to identify a hormone treatment, using a rat as the model organism, may need to cast a wider net. The aim of this

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<sup>1</sup> Haddaway, Neal Robert and Biljana Macura. "The Role of Reporting Standards in Producing Robust Literature Reviews." *Nature Climate Change* 8, no. 6 (2018): 444-47. <http://dx.doi.org/10.1038/s41558-018-0180-3>

Uman, Lindsay S. "Systematic Reviews and Meta-Analyses." *Journal of the Canadian Academy of Child and Adolescent Psychiatry* 20, no. 1 (2011): 57-59. <https://www.ncbi.nlm.nih.gov/pubmed/21286370>

<sup>2</sup> Holy, Timothy E. and Zhongsheng Guo. "Ultrasonic Songs of Male Mice." *PLOS Biology* 3, no. 12 (2005): e386. <http://dx.doi.org/10.1371/journal.pbio.0030386>

research is not specific to rats, but is an effort to more broadly understand a biological process. A systematic review should include hormone studies in a variety of species under a more broadly defined set of search terms. Literature review might include the results of metabolic and molecular analyses of hormones themselves, as well as reviews of unpublished, sometimes unfavorable, results. This type of analysis constitutes systematic review. Increasingly, systematic review also involves some form of meta-analysis. Meta-analysis is defined as the use of tools to compare all data within a systematic review to identify commonalities and disparities.<sup>1</sup> For example, a meta-analysis of all experiments across several species may or may not show that these studies yield the same result. This sort of analysis helps determine if the line of inquiry has enough merit to warrant further investigation, thus reducing the total number of animals required in entire fields of study. Meta-analysis across species can also be an indicator of the translational potential of an intervention for human use.<sup>2</sup>

A clinical trial has a direct impact on the health and livelihood of human participants. For this reason, systematic review provides critical input into the design of any trial. Over 170 medical journals have adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist as a prerequisite for publishing consideration.<sup>3</sup> The list includes

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<sup>1</sup> Hooijmans, Carlijn R., Joanna Int'Hout, Merel Ritskes-Hoitinga, and Maroeska M. Rovers. "Meta-Analyses of Animal Studies: An Introduction of a Valuable Instrument to Further Improve Healthcare." *ILAR Journal* 55, no. 3 (2014): 418-26. <http://dx.doi.org/10.1093/ilar/ilu042>

<sup>2</sup> Fay, Michael P., Dean A. Follmann, Freyja Lynn, Jarad M. Schiffer, Gregory V. Stark, Robert Kohberger, Conrad P. Quinn, and Edwin O. Nuzum. "Anthrax Vaccine-Induced Antibodies Provide Cross-Species Prediction of Survival to Aerosol Challenge." *Science Translational Medicine* 4, no. 151 (2012): 151ra26. <http://stm.sciencemag.org/content/4/151/151ra126.abstract>

Hooijmans, "Meta-Analyses of Animal Studies: An Introduction of a Valuable Instrument to Further Improve Healthcare," 5.

<sup>3</sup> PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. "Endorse PRISMA." Copyright 2015 PRISMA (accessed 2018). <http://PRISMA-statement.org/Endorsement/EndorsePRISMA111>

such notable journals as The Lancet, The Journal of the American Medical Association (or JAMA), and The British Medical Journal (BMJ).<sup>1</sup>

However, research has shown an apparent lack of systematic review in preclinical animal trials.<sup>2</sup> Many, such as Peters and colleagues, cite the lack of meta-analysis informing study design as detrimental to the validity of research results, having profound downstream effects on subsequent clinical trials.<sup>3</sup>

In some fields, such as toxicology, conducting human subject trials are neither ethical nor feasible due to lethal or physical risk. Such studies may fall under the Food and Drug Administration's "Animal Rule," which allows for the marketing of substances not tested in a clinical setting.<sup>4</sup> This raises safety concerns for direct to market chemicals tested only in vertebrate trials, where comprehensive systematic analyses are less common.

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<sup>1</sup> PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. "PRISMA Endorsers." Copyright 2015 PRISMA (accessed 2018). <http://PRISMA-statement.org/Endorsement/PRISMAEndorsers#d>

<sup>2</sup> Hooijmans, Carlijn R. R., Leenaars, Marlies and Merel Ritskes-Hoitinga. "A Gold Standard Publication Checklist to Improve the Quality of Animal Studies, to Fully Integrate the Three Rs, and to Make Systematic Reviews More Feasible." *Altern Lab Anim* 38, no. 2 (May 2010): 167-82.

Henderson, Valerie C., Jonathan Kimmelman, Dean Fergusson, Jeremy M. Grimshaw, and Dan G. Hackam. "Threats to Validity in the Design and Conduct of Preclinical Efficacy Studies: A Systematic Review of Guidelines for in Vivo Animal Experiments." *PLOS Medicine* 10, no. 7 (2013): e1001489. <http://dx.doi.org/10.1371/journal.pmed.1001489>

Hooijmans Carlijn R. and Merel Ritskes-Hoitinga. "Progress in Using Systematic Reviews of Animal Studies to Improve Translational Research." *PLOS Medicine* 10, no. 7 (2013): e1001482. <http://dx.doi.org/https://doi.org/10.1371/journal.pmed.1001482>

<sup>3</sup> Peters, Jaime L. , Alex J. Sutton, David R. Jones, Lesley Rushton and Keith R. Abrams. "A Systematic Review of Systematic Reviews and Meta-Analyses of Animal Experiments with Guidelines for Reporting." *J Environ Sci Health B* 41, no. 7 (2006): 1245-58. <http://dx.doi.org/10.1080/10934520600655507>

<sup>4</sup> FDA, Food and Drug Administration. *Product Development under the Animal Rule, Guidance for Industry* Edited by U.S. Department of Health and Human Services; Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER): 2015. <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm399200.htm>



The introduction of systematic review as common practice in animal trials will help avoid unnecessary human clinical trials on otherwise ineffective, or potentially harmful, treatments. Other benefits include decreased variation between similar trials, more reliable and reproducible results, reduction in the number of animals needed, cost-benefits, and standardization of practices.<sup>1</sup>

In 2011, The National Academies hosted a conference entitled “U.S. and European Animal Research Regulations: Impact on Neuroscience Research.” The goals of the workshop included an examination of the current regulatory environment, scientific trends, and a needs assessment. A topic of particular interest at the forum was the benefit of systematic review in the design of a vertebrate animal protocol. Workshop participants cited the apparent lack of systematic review in vertebrate animal trials as problematic. Their recommendations for implementing the widespread practice of systematic review include engaging key influencers such as “[The] Food and Drug Administration, pharmaceutical companies, research institutions, and publishers.”<sup>2</sup>

### 1.3. Questions to be addressed

This report addresses two central questions: i.) what issues must be addressed before an institution can promote systematic review? and ii.) what practices can be implemented to encourage systematic review in the development of animal protocols? These two questions will

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<sup>1</sup>Hooijmans, "A Gold Standard Publication Checklist to Improve the Quality of Animal Studies, to Fully Integrate the Three Rs, and to Make Systematic Reviews More Feasible," 6.

<sup>2</sup> Institute of Medicine and National Research Council. *International Animal Research Regulations: Impact on Neuroscience Research: Workshop Summary*. edited by E. Pankevich Diana, M. Wizemann Theresa, Mazza Anne-Marie, and M. Altevogt Bruce. Washington, DC: The National Academies Press, 2012.

be addressed by examining four aspects of a research institution: culture, administration, training, and public policy.

#### 1.4. Objectives

In the United States, the Institutional Animal Care and Use Committee (IACUC) provides an opportunity for institutions of higher education to encourage the incorporation of systematic reviews in vertebrate animal research. It requires expanding the animal program beyond the committee. This report provides an overview of the benefits of systematic review, discusses the regulatory and institutional environment influencing conduct of an IACUC, and demonstrates how an institution can promote systematic review as a best practice for animal protocol development.

#### 1.5. Significance

Many animal trials are a key component of translational research efforts. These are defined as preclinical studies of interventions in vertebrate animals, leading to later clinical trials in human beings. However, the notable lack of systematic review in preclinical animal trials leads to many challenges. These include repetition of protocols that have been already proven ineffective, and commencing clinical trials in human subjects on otherwise ineffective interventions. Also cited is an apparent lack of publication of negative results, which has the potential to introduce bias in subsequent research efforts.<sup>1</sup>

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<sup>1</sup> Hooijmans, Carlijn R., Joanna Int'Hout, Merel Ritskes-Hoitinga, and Maroeska M. Rovers. "Meta-Analyses of Animal Studies: An Introduction of a Valuable Instrument to Further Improve Healthcare." *ILAR Journal* 55, no. 3 (2014): 418-26. <http://dx.doi.org/10.1093/ilar/ilu042>.

The biomedical community is actively engaged in improving methods for comprehensive systematic review. This is evidenced in the activities of organizations such as the CONSORT Group (Consolidated Standards of Reporting Trials),<sup>1</sup> the Cochrane Library,<sup>2</sup> and CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies).<sup>3</sup> These efforts focus on the convergence of big data management, digital innovation, and the desire to improve both vertebrate preclinical and human clinical trials research. Given the benefits and significance of systematic review in clinical trials research, expanding the practice in vertebrate animal trials is a logical step forward.

### 1.6. Exclusions and limitations

There are limitations in the implementation of systematic review and meta-analysis in animal research. These include administrative burden,<sup>4</sup> lack of negative results in publication,<sup>5</sup> and the conflict between academic freedom and institutional oversight.<sup>6</sup> Negative results are the

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<sup>1</sup> CONSORT. "Consolidated Standards of Reporting Trials " Last modified 2018 (accessed 2018.) <http://www.consort-statement.org/>

<sup>2</sup> Cochrane. "The Cochrane Library." (accessed 2018). <https://www.cochranelibrary.com/>

<sup>3</sup> CAMARADES "Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies." Last modified 2018 (accessed 2018). <http://www.dcn.ed.ac.uk/camarades/default.htm>

<sup>4</sup> FASEB, The Federation of American Societies for Experimental Biology, AAMC, The Association of American Medical Colleges, COGR, The Council on Governmental Relations, and NABR, The National Association for Biomedical Research. "Reforming Animal Research Regulations: Workshop Recommendations to Reduce Regulatory Burden." (2017). <http://www.faseb.org/Portals/2/PDFs/opa/2017/FASEB-Animal-Regulatory-Report-October2017.pdf>

<sup>5</sup> Hooijmans, "Progress in Using Systematic Reviews of Animal Studies to Improve Translational Research," 6.

Haddaway, "The Role of Reporting Standards in Producing Robust Literature Reviews." 4.

<sup>6</sup> *The Care and Feeding of an IACUC: The Organization and Management of an Institutional Animal Care and Use Committee*. Boca Raton: CRC Press, 1999.

Everitt, Jeffrey I. and Brian. R. Berridge. "The Role of the IACUC in the Design and Conduct of Animal Experiments That Contribute to Translational Success." *ILAR Journal* 58, no. 1 (2017): 129-34. <http://dx.doi.org/10.1093/ilar/ilx003>.

least likely to be published. Such publication bias makes systematic review challenging for researchers.<sup>1</sup> Furthermore, a systematic review, by design, is a “synthesis” of the results of all studies published on any given topic. Therefore, difficulty in conducting a comprehensive review is largely due to the amount of effort required.<sup>2</sup>

Finally, faculty policies on academic freedom are at odds with any administrative attempts to mandate a single scientific approach.<sup>3</sup> For these reasons, any interest in institutionally promoting systematic review must begin with an understanding of systematic review and how it was introduced in the field of medicine.

## Chapter 2. Review of the Literature

### 2.1. Overview of literature review

This report documents ways in which an institution can promote systematic review as a best practice, thus improving the quality of animal research. There are four types of literature reviewed in the conduct of this exercise.

Firstly is a review of the literature on systematic review itself. Within the literature on systematic review, are two subgroups; a.) systematic review in human trials, and b.) systematic

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<sup>1</sup> Korevaar, D. A., L. Hooft, and G. ter Riet. "Systematic Reviews and Meta-Analyses of Preclinical Studies: Publication Bias in Laboratory Animal Experiments." *Lab Anim* 45, no. 4 (2011): 225-30. <http://dx.doi.org/10.1258/la.2011.010121>

Briel, Matthias, Katharina F. Müller, Joerg J. Meerpohl, Erik von Elm, Britta Lang, Edith Motschall, Viktoria Gloy, Francois Lamontagne, Guido Schwarzer, and Dirk Bassler. "Publication Bias in Animal Research: A Systematic Review Protocol." *Systematic Reviews* 2 (2013): 23-23. <http://dx.doi.org/10.1186/2046-4053-2-23>

<sup>2</sup> Uman, "Systematic Reviews and Meta-Analyses," 4.

<sup>3</sup> Prentice, Ernest D., David A. Crouse, and Michael D. Mann. "Scientific Merit Review: The Role of the IACUC" *ILAR News* 34, no. 1-2 (1992).

review as it relates to preclinical [animal] trials. Topics covered include systematic review, meta-analysis, and publication bias.

Secondly, literature concerning the conduct and requirements of an IACUC are reviewed. These include both scientific publications researching the conduct of the IACUC, as well as industry publications about IACUC functionality. Additionally, regulations governing the conduct of an IACUC and institutional compliance are reviewed. The regulatory landscape surveyed for this exercise is largely that of the United States, because of its relevance to the author.

Thirdly, the report includes a survey of tools that serve not only as models for best practice, but might be utilized by an institution too help promote systematic review and meta-analysis more formally and as a matter of institutional policy. These include publication checklists, reports, data repositories, and training models for faculty development.

Finally, regulatory and policy documents are examined. This includes U.S. Federal rules and regulations, as well as publications such as *The Milbank Quarterly*, which provide peer reviewed literature on topics of policy and health management.<sup>1</sup>

## 2.2. Literature used to inform this report

Literature review for this report was conducted using a number of methods. Google Scholar and Johns Hopkins Sheridan Library were used to identify academic papers on the topic of translational research, systematic review, and IACUC. Additionally, publications and reports from professional organizations such as the Federation of American Societies for Experimental Biology (FASEB) were investigated. Also reviewed were the practices of organizations that

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<sup>1</sup> The Milbank Quarterly, Milbank. *The Milbank Quarterly*. edited by Alan B. Cohen, Christopher F. Koller, and Tara Strome. New York, NY 10022, 2018.

promote systematic review in both human and animal sciences such as the Cochrane Database of Systematic Reviews (Cochrane) and the National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs).<sup>1</sup>

### *2.2.1 Publications most relevant: Systematic review and meta-analysis*

- Briel, M., K. F. Müller, J. J. Meerpohl, E. von Elm, B. Lang, E. Motschall, V. Gloy, F. Lamontagne, G. Schwarzer, and D. Bassler. "Publication Bias in Animal Research: A Systematic Review Protocol." *Systematic Reviews* 2 (2013): 23-23. <http://dx.doi.org/10.1186/2046-4053-2-23>
- Haddaway, N. R. and B. Macura. "The Role of Reporting Standards in Producing Robust Literature Reviews." *Nature Climate Change* 8, no. 6 (2018): 444-47. <http://dx.doi.org/10.1038/s41558-018-0180-3>.
- Henderson, V. C., J. Kimmelman, D. Fergusson, J. M. Grimshaw, and D. G. Hackam. "Threats to Validity in the Design and Conduct of Preclinical Efficacy Studies: A Systematic Review of Guidelines for in Vivo Animal Experiments." *PLOS Medicine* 10, no. 7 (2013): e1001489. <http://dx.doi.org/10.1371/journal.pmed.1001489>
- Hooijmans C. R. and M. Ritskes-Hoitinga. "Progress in Using Systematic Reviews of Animal Studies to Improve Translational Research." *PLOS Medicine* 10, no. 7 (2013): e1001482. <http://dx.doi.org/https://doi.org/10.1371/journal.pmed.1001482>.
- Hooijmans, C. R., M. Leenaars, and M. Ritskes-Hoitinga. "A Gold Standard Publication Checklist to Improve the Quality of Animal Studies, to Fully Integrate the Three Rs, and to Make Systematic Reviews More Feasible." *Altern Lab Anim* 38, no. 2 (May 2010): 167-82.
- Hooijmans, C. R., J. IntHout, M. Ritskes-Hoitinga, and M. M. Rovers. "Meta-Analyses of Animal Studies: An Introduction of a Valuable Instrument to Further Improve Healthcare." *ILAR Journal* 55, no. 3 (2014): 418-26. <http://dx.doi.org/10.1093/ilar/ilu042>
- Korevaar, D. A., L. Hooft, and G. ter Riet. "Systematic Reviews and Meta-Analyses of Preclinical Studies: Publication Bias in Laboratory Animal Experiments." *Lab Anim* 45, no. 4 (Oct 2011): 225-30. <http://dx.doi.org/10.1258/la.2011.010121>
- Peters, J. L., A. J. Sutton, D. R. Jones, L. Rushton, and K. R. Abrams. "A Systematic Review of Systematic Reviews and Meta-Analyses of Animal Experiments with Guidelines for

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<sup>1</sup> Cochrane. "The Cochrane Library." (accessed 2018). <https://www.cochranelibrary.com/>

NC3Rs. "National Centre for the Replacement, Refinement, and Reduction of Animals in Research." Last modified 2018 (accessed 2018). <https://www.nc3rs.org.uk/>

Reporting." J Environ Sci Health B 41, no. 7 (2006): 1245-58.  
<http://dx.doi.org/10.1080/10934520600655507>

Smalheiser, N. R. and A. M. Cohen. "Text Mining Pipeline to Accelerate Systematic Reviews in Evidence-Based Medicine." HHS/National Library of Medicine (NLM) Award No. 5R01LM010817-06 (2017).

[https://projectreporter.nih.gov/project\\_info\\_details.cfm?aid=9310440](https://projectreporter.nih.gov/project_info_details.cfm?aid=9310440)

van Luijk, J., B. Bakker, M. M. Rovers, M. Ritskes-Hoitinga, R. B. M. de Vries, and M. Leenaars. "Systematic Reviews of Animal Studies; Missing Link in Translational Research?" PLoS One 9, no. 3 (2014): e89981.  
<http://dx.doi.org/10.1371/journal.pone.0089981>

### *2.2.2 Publications most relevant: Functions and concerns of the IACUC*

The Care and Feeding of an IACUC: The Organization and Management of an Institutional Animal Care and Use Committee. Boca Raton: CRC Press, 1999.

Bronstad, A. and A. G. Berg. "The Role of Organizational Culture in Compliance with the Principles of the 3rs." Lab Anim (NY) 40, no. 1 (2011): 22-6.  
<http://dx.doi.org/10.1038/labani0111-22>

Everitt, J. I. and B. R. Berridge. "The Role of the IACUC in the Design and Conduct of Animal Experiments That Contribute to Translational Success." ILAR Journal 58, no. 1 (2017): 129-34. <http://dx.doi.org/10.1093/ilar/ilx003>

NRC, National Research Council. Guide for the Care and Use of Laboratory Animals. Edited by National Research Council (U.S.), Institute for Laboratory Animal Research (U.S.), and National Academies Press (U.S.). 8th ed. Washington, D.C.: National Academies Press, 2011. <http://www.ncbi.nlm.nih.gov/books/NBK54050>

The Public Health Service Responds to Commonly Asked Questions: 7. To What Extent, If Any, Is the IACC Responsible for Assessing the Scientific Merit of Proposals It Reviews?, by OLAW Office of Laboratory Animal Welfare, OLAW, last updated on February 11, 2008. <https://grants.nih.gov/grants/olaw/references/ilar91.htm>

FASEB, The Federation of American Societies for Experimental Biology, AAMC, The Association of American Medical Colleges, COGR, The Council on Governmental Relations, and NABR, National Association for Biomedical Research. "Reforming Animal Research Regulations: Workshop Recommendations to Reduce Regulatory Burden." (2017). <http://www.faseb.org/Portals/2/PDFs/opa/2017/FASEB-Animal-Regulatory-Report-October2017.pdf>

Silverman, J., C. W. Lidz, J. C. Clayfield, A. Murray, L. J. Simon, and R. G. Rondeau. "Decision Making and the IACUC: Part 1—Protocol Information Discussed at Full-Committee

Reviews." J Am Assoc Lab Anim Sci 54, no. 4 (2015): 389-98.  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4521573/>  
 Prentice, E. D., D. A. Crouse, and M. D. Mann. "Scientific Merit Review: The Role of the IACUC." ILAR News 34, no. 1-2 (Winter-Spring 1992): 15-9.  
 OLAW, Office of Laboratory Animal Welfare. "Public Health Service Policy on Humane Care and Use of Laboratory Animals." (Revised 2015).  
<https://grants.nih.gov/grants/olaw/references/phspol.htm#AnimalWelfareAssurance>

### *2.2.3 Publications most relevant: Implementation of best practices*

Alhaider, S. A., H. A. Alshehri, and S. A. Almedhesh. "Research Training, Productivity and Challenges among Trainees of Pediatric Residency Programs across Saudi Arabia." International Journal of Pediatrics and Adolescent Medicine 2, no. 2 (2015): 70-74.  
<http://dx.doi.org/https://doi.org/10.1016/j.ijpam.2015.06.005>  
 FASEB Federation of American Societies for Experimental Biology, FASEB. Enhancing Research Reproducibility: Recommendations from the Federation of American Societies for Experimental Biology 2016.  
 Frankel, M.S. "Professional Codes: Why, How, and with What Impact?" Journal of Business Ethics 8, no. 2-3 (February 1989 1989): 109-15. <http://dx.doi.org/DOI>  
 Haras, C. "Faculty Development as an Authentic Professional Practice." Higher Education Today (2018). <https://www.higheredtoday.org/2018/01/17/faculty-development-authentic-professional-practice/>  
 Haywood, J. R. and M. Greene. "Avoiding an Overzealous Approach: A Perspective on Regulatory Burden." ILAR j 49, no. 4 (2008): 426.  
 Jefcoat, A. M. "The 'Triad of Noncompliance' as a Tool for Understanding, Preventing and Correcting Protocol and Procedural Noncompliance." Lab Anim. (NY) 37 (2008): 459-63.  
 Levin, S. I., C. Malinowski, and D. M. Palila Berger. "Response to Protocol Review: Help IACUC Understand the Science." Lab Animal 39 (2010): 260.  
<http://dx.doi.org/10.1038/labani0910-260b>  
 Pescina Liberale, A. and J. V. Kovach. "Reducing the Time for IRB Reviews: A Case Study." Journal of Research Administration 48, no. 2 (2017): 37-50.  
[http://download.srainternational.org/journal/archive/JRA\\_V48n2-2017.pdf](http://download.srainternational.org/journal/archive/JRA_V48n2-2017.pdf)  
 Prentice, E. D., M. E. Blackburn, and R. S. Dixon. "Fostering Collaborative Roles and Responsibilities for Members of an IACUC or Oversight Body." In Management of Animal Care and Use Programs in Research, Education, and Testing, edited by nd, R. H. Weichbrod, G. A. H. Thompson, and J. N. Norton, 27-34. Boca Raton (FL): CRC Press/Taylor & Francis Group, LLC., 2018.



Sorcinelli, M. D. "Faculty Development: The Challenge Going Forward." Peer Review, Association of American Colleges & Universities 9, no. 4 (2007).  
<https://www.aacu.org/publications-research/periodicals/faculty-development-challenge-going-forward>.

Webster-Wright, A. Authentic Professional Learning: Making a Difference through Learning at Work. Vol. 2. Professional and Practice-Based Learning: Springer, 2010.

#### *2.2.4 Publications most relevant: Public policy and regulation*

89-544, P.L. The Animal Welfare Act (Laboratory Animal Welfare Act of 1966, P.L. 89-544). 1966.

FDA, Food and Drug Administration. Product Development under the Animal Rule, Guidance for Industry Edited by U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER): 2015.

Fox, D. M. "Evidence of Evidence-Based Health Policy: The Politics of Systematic Reviews in Coverage Decisions." Health Aff (Millwood) 24, no. 1 (Jan-Feb 2005): 114-22.  
<http://dx.doi.org/10.1377/hlthaff.24.1.114>.

Fox, D. M. "Systematic Reviews and Health Policy: The Influence of a Project on Perinatal Care since 1988." Milbank Q 89, no. 3 (Sep 2011): 425-49. <http://dx.doi.org/10.1111/j.1468-0009.2011.00635.x>

NCCPE, National Co-ordinating Centre for Public Engagement, UK. "What Does an Engaged University Look Like?" About engagement (2018).  
<http://www.publicengagement.ac.uk/about-engagement/what-does-engaged-university-look>

### **2.3. Relevance**

Many publications on the subject demonstrate both the benefits and challenges of systematic review. This literature helps to not only understand what it is to conduct a systematic review, but also examines the frequency of such reviews the field of animal research. Specific metrics on the utilization of systematic review in animal research, instances of publication bias, and trends in animal research will be summarized.

Literature on the subject of the IACUC includes both scientific analysis of the conduct of an IACUC as well as regulations, policies, and reports. Relevant topics include a review of

IACUC discussions, the administrative burden associated with animal compliances, as well as the competing interest between academic freedom and an IACUC's imperative to improve animal research protocols. Studies on the conduct of an IACUC help to demonstrate common topics of discussion in IACUC review, their composition of committees, and their current practices. Regulatory and policy documents help understand the legal and institutional responsibilities of the IACUC. Other literature provides an understanding of the challenges facing an IACUC such as high turnover and large workloads.

Researching those tools available to institutions helps inform the recommendations in this report. The tools described provide resources for institutions that will aid in the promotion of systematic review as routine best practice. Some resources provide solutions in related areas of research administration, that give insight into how one might approach training, administration, and conduct of a more comprehensive animal care program at their institution.

Lastly is research on public policy, specifically as it relates to healthcare management and the introduction of systematic review as common practice in medicine. This literature demonstrates how systematic review was implemented as a common practice in medicine, and how the healthcare community engages with policymakers.

### **Chapter 3. Needs assessment**

#### **3.1. Metrics and Needs Establishment**

Analysts in the field of preclinical biomedical sciences have identified publication bias and lack of systematic review informing study design as two major concerns. In a 2006 analysis of 103 publications in the field of in-vivo animal experimentation, *Peters et.al.* found that only 84% reported any type of systematic review informing their study design and only 17% reported

conducting meta-analyses.<sup>1</sup> They cite inherent problems with the lack of meta-analysis in particular:

The inadequate reporting of meta-analyses observed here leads to questions on whether the most appropriate methods were used to maximize the use of the animal evidence to inform policy or decision-making.

Of the 86 articles identified as including some form of systematic review, only 52 reported searching for prior results in both animal and human research.

In 2013 *Henderson et. al.* reviewed recommendations for preclinical experimental design in the publishing community and found virtually no recommendations for systematic review in their sample set:<sup>2</sup>

We initially set out to capture guidelines addressing two levels of preclinical observation: individual experiments and aggregation of multiple experiments (i.e., systematic review of preclinical efficacy studies). However, because we were unable to identify a critical mass of guidelines addressing aggregation [...], we could not advance these guidelines to extraction.

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<sup>1</sup> Peters, "A Systematic Review of Systematic Reviews and Meta-Analyses of Animal Experiments with Guidelines for Reporting," 6.

<sup>2</sup> Henderson, Valerie C., Jonathan Kimmelman, Dean Fergusson, Jeremy M. Grimshaw, and Dan G. Hackam. "Threats to Validity in the Design and Conduct of Preclinical Efficacy Studies: A Systematic Review of Guidelines for in Vivo Animal Experiments." *PLOS Medicine* 10, no. 7 (2013): e1001489. <http://dx.doi.org/10.1371/journal.pmed.1001489>

These two studies demonstrate the lack of systematic review as a common practice among researchers, but also demonstrate a lack of proper guidance on the conduct of such analyses. Of those systematic reviews reported, many still failed to meet the requirements needed to demonstrate experimental “validity.”<sup>1</sup>

It has been noted that academic journals can increase the practice of systematic review through the requirement of transparency and data sharing.<sup>2</sup> This is becoming increasingly less burdensome with advancements in data storage and sharing capabilities.

In a 2011 observation of 87 IACUC protocol review discussions, researchers found that conversation about preliminary data review was virtually non-existent. When discussed, IACUCs focus largely on prior literature to evaluate alternatives to reduce pain and distress (14 mentions out of a total 87 protocol reviews recorded). Of the 17 identified topics of IACUC conversation, the three topics least likely to be discussed were “importance of research,” “alternatives to animals,” and “preliminary data.”<sup>3</sup>

This lack of attention to prior literature can be partially attributed to a regulatory “gap” which recommends, but does not mandate, systematic review and meta-analysis when drafting an animal protocol. For example, the Guide’s definition of the word “should” gives institutions some measure of flexibility.

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<sup>1</sup> Briel, “Publication Bias in Animal Research: A Systematic Review Protocol,” 9.

van Luijk, Judith, Brenda Bakker, Maroeska M. Rovers, Merel Ritskes-Hoitinga, Rob B. M. de Vries, and Marlies Leenaars. “Systematic Reviews of Animal Studies; Missing Link in Translational Research?” *PLoS One* 9, no. 3 (2014): e89981. <http://dx.doi.org/10.1371/journal.pone.0089981>

<sup>2</sup> Hooijmans, “Progress in Using Systematic Reviews of Animal Studies to Improve Translational Research,” 6.

<sup>3</sup> Silverman, Jerald, Charles W. Lidz, Jonathan C. Clayfield, Alexandra Murray, Lorna J. Simon, and Richard G. Rondeau. “Decision Making and the IACUC: Part 1—Protocol Information Discussed at Full-Committee Reviews.” *J Am Assoc Lab Anim Sci* 54, no. 4 (2015): 389-98. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4521573/>

*Must* indicates actions that the Committee for the Update of the *Guide* considers imperative and mandatory duty or requirement for providing humane animal care and use. *Should* indicates a strong recommendation for achieving a goal; however, the Committee recognizes that individual circumstances might justify an alternative strategy. *May* indicates a suggestion to be considered.<sup>1</sup>

Arguably, research institutions also have a role to play in the promotion of systematic review in animal experimental design. In addition to the regulatory imperative to protect animal subjects, it is the responsibility of institutions to eliminate “waste, fraud, and abuse” of federal funds. Additionally, all institutions of higher education have an academic code, aiming to promote health, education, and prosperity among the communities that they serve. Creating a culture of sound scientific practice can assist with these goals.

## Chapter 4: Project Description

### 4.1 Description of project elements

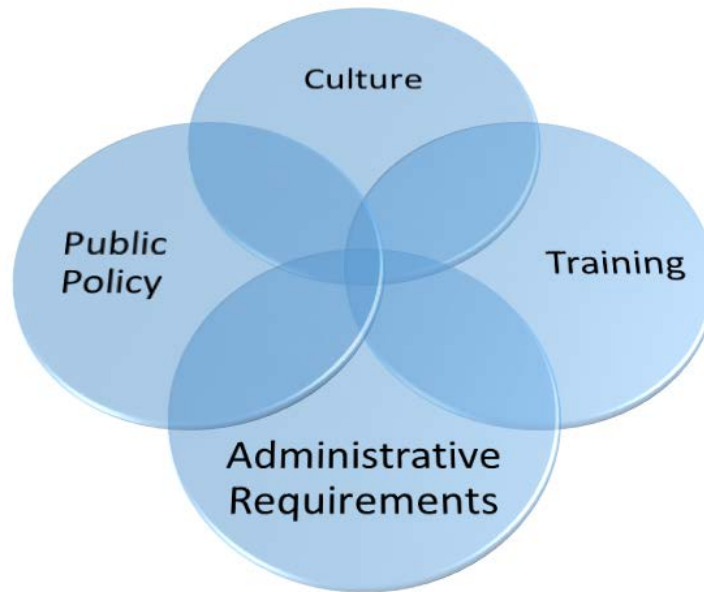
Recommendations for implementing the widespread practice of systematic review include engaging key influencers, including research institutions.<sup>2</sup> Institutions of Higher Education have an opportunity to encourage the incorporation of systematic review in vertebrate animal research. This report investigates four spheres of influence that, in combination, effect any research environment. These four factors are summarized as cultural, administrative, policy,

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<sup>1</sup> NRC, National Research Council, *Guide for the Care and Use of Laboratory Animals*, 2.

<sup>2</sup> Institute of Medicine, *International Animal Research Regulations: Impact on Neuroscience Research: Workshop Summary*, 7.

and training-related. When effectively managed, these four elements help the institution achieve research excellence.



**Figure 1.1.** Four spheres institutional influence. Overlapping areas have the potential to be problematic, but also offer opportunities.

However, intersection between these four elements can be problematic. Reactionary measures and mission creep serve as examples of pain points in each intersecting sphere. This report investigates those areas where each influence overlaps, in an effort to identify both pain points and solutions.

This report will help institutions encourage systematic review through pro-active shifts in culture, training opportunities, and ways of re-framing the IACUC review process. Recommendations include building an “outward-facing” animal program that extends beyond the IACUC and the Attending Veterinarian. Engaging policy makers and organizational change-management strategies are also discussed.

## Chapter 5. Methodology

### 5.1. Project Design

This report specifically examines the administrative and cultural aspects of the institution, in relation to vertebrate animal policy and training. Recommendations will be presented utilizing these four intersecting elements.

#### *5.1.1 Examination of institutional culture*

Examining the cultural challenges facing the health sector when systematic review was first introduced will provide some perspective for animal research programs. Additionally, the relationship between faculty and administrative offices is examined. Central questions to be addressed include: a.) what is the relationship between faculty and administration? b.) when does academic freedom intersect with institutional requirements? c.) how do institutions engage faculty at these intersections?

#### *5.1.2 Examination of the administrative environment*

In order to address the administrative environment, those areas where policy and administrative requirements intersect will be examined. Similarly, an examination of administrative requirements and training activities will be explored. This requires examination of federally mandated requirements and institutional interpretation of those requirements. Central questions to be addressed include: a.). what is the function and role of the IACUC? b.) how can IACUCs improve their practices in order to promote scientific excellence? c.) how can an institution engage faculty with limited administrative burden?

#### *5.1.3 Examination of training and development*

Once these challenges have been identified, a critical analysis of subsequent solutions, and their outcomes will be identified. Those solutions with the most promising outcome are

suggested for further implementation. Central questions include: a.) how do institutions implement compliance training? b.) are these methods effective? c.) what role do faculty play in the execution of training programs? d.) how might an institution engage faculty in order to promote best practices? e.) what role does the institution play in training the next generation of scientists?

#### *5.1.4 Examination of science and policy*

Policymakers are stakeholders as well as key influencers. Further insight is drawn from groups who conduct regular analysis and public policy recommendations, such as the Council on Governmental Relations (COGR), The Federation of American Societies for Experimental Biology (FASEB), the Milbank group, and others.<sup>1</sup> Central questions include: a.) what role do policy makers play in the promotion of the sciences? b.) how do institutions implement policy at the local level in response to regulation? and c.) what can institutions do to engage policy makers?

## **Chapter 6. Project Results and Discussion**

### **6.1 Results and Discussion**

#### *6.1.1 Discussion of cultural elements*

There is an apparent tension between the interpretation of an IACUC's function and its influence on experimental design. The Guide specifically states that an IACUC's function is not to comment on the scientific merit of a protocol; however, this is in contrast to the requirement to evaluate the merits of "population size," "hypothesis testing," and "adequacy of controls:"

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<sup>1</sup> COGR, *Council on Governmental Relations*. <https://www.cogr.edu/> (accessed, 2018).

FASEB, *The Federation of American Societies for Experimental Biology*. <http://www.faseb.org/> (accessed, 2018).

*The Milbank group* <https://www.milbank.org/> (accessed, 2018).



While the responsibility for scientific merit review normally lies outside the IACUC, the committee members should evaluate scientific elements of the protocol as they relate to the welfare and use of the animals.<sup>1</sup>

There are those faculty who feel that the IACUC is not scientifically expert enough to comment on the scientific merit of a project. They see this not only as an insult to their expertise, but an unnecessary bureaucratic infringement on their academic freedom.<sup>2</sup> Similarly, OLAW has clarified that “peer review of the scientific merit of a proposal is considered to be the purview of the PHS funding component,” and suggests that the “primary focus of the IACUC is animal welfare.”<sup>3</sup> However, even they recognize that a clear distinction is not practicable. They cite PHS policy, which asks IACUCs to consider “relevance to human or animal health, the advancement of knowledge, or the good of society.”<sup>4</sup> This demonstrates another area where it is largely up to institution to interpret the scope of their “merit” evaluation. Stephen Levin and colleagues at the Northwestern Center for Comparative Medicine, address this concern by suggesting a compromise:

In our opinion, IACUCs should limit their scientific and technical review of animal research projects to those that have not undergone a critical peer review process, those in which serious potential animal welfare issues

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<sup>1</sup> NRC, National Research Council. *Guide for the Care and Use of Laboratory Animals*, 2.

<sup>2</sup> Prentice, "Scientific Merit Review: The Role of the IACUC," 10.

<sup>3</sup> *The Public Health Service Responds to Commonly Asked Questions: 7. To What Extent, If Any, Is the IACUC Responsible for Assessing the Scientific Merit of Proposals It Reviews?*, by OLAW Office of Laboratory Animal Welfare, OLAW, last updated on February 11, 2008. <https://grants.nih.gov/grants/olaw/references/ilar91.htm>

<sup>4</sup> OLAW, Office of Laboratory Animal Welfare, *Public Health Service Policy on Humane Care and Use of Laboratory Animals*, 3.

exist and those suffering from an egregious omission of a valid scientific point.

Indeed, others have suggested that applications that have already undergone two rounds of review by the NIH have already been vetted,<sup>1</sup> but this begs the question, how much peer review discussion involves the “appropriateness” of the animal or the experiment? Lack of any sort of review of this type by the IACUC might inadvertently promote poor scientific practices. This is a direct concern of the International Council for Laboratory Animal Science (ICLAS). They state their concern that poor scientific methods are “perpetuated by virtue of being previously published.”<sup>2</sup> Arguably, an experiment could meet all of the meritorious requirements of the peer review panel, but still not rise to the level of the highest scientific standards. Therefore, it is evident that the IACUC must play some part in the review of the scientific rigor of the experiment.

The recognition of administrative burden is in direct contrast with the need for systematic review to occur more frequently in animal protocol development. However, this is because literature review has been represented largely as a regulatory or institutional requirement and not promoted as a natural facet of the scientific approach. The medical field provides an opportunity to examine this paradigm shift more thoroughly.

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<sup>1</sup> Levin, Stephen I., Carolyn Malinowski, and Diana M. Palila Berger. "Response to Protocol Review: Help IACUC Understand the Science." *Lab Animal* 39 (2010): 260. <http://dx.doi.org/10.1038/labon0910-260b>

<sup>2</sup> ICLAS, The International Council for Laboratory Animal Science. "Guidelines for Researchers." Last modified 2012 (accessed 2018). <http://iclas.org/guidelines-for-researchers>

In a 2011 retrospective entitled “Systematic Reviews and Health Policy,” Daniel Fox describes the introduction of systematic review in the field of prenatal care.<sup>1</sup> Fox demonstrates some of the language used by proponents of systematic review and the subsequent reaction of the medical community.

The Effective Care in Pregnancy and Childbirth (ECPC) Project consisted of a series of four systematic reviews of the body of evidence in the field of prenatal care. Two primary linguistic styles, or “rhetoric,” were employed in these reports. For example, Archie Cochrane of the Cochrane group, an early supporter of systematic review, tended to use language that Fox describes as “polemic.” This polemic tone is one that claims superiority by denouncing the status quo, followed by strong language in support of the desired change:

[Cochrane] repeated an accusation he had made in 1979, that obstetricians made the “worst” use of randomized controlled trials among medical specialists. Then he proclaimed that the systematic reviews were a “new achievement” and a “milestone.”<sup>2</sup>

Understandably, this tone was met with much resistance from the established medical community. The report was interpreted as an affront to their hard work and field experience. The statistical results of the review indicated that some commonly adopted practices were often ineffective, inconsistent, or unhealthy. This was also met with resistance from current

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<sup>1</sup> Fox, Daniel. M. "Systematic Reviews and Health Policy: The Influence of a Project on Perinatal Care since 1988." *Milbank Q* 89, no. 3 (Sep 2011): 425-49. <http://dx.doi.org/10.1111/j.1468-0009.2011.00635.x>

<sup>2</sup> Fox, "Systematic Reviews and Health Policy," 24.

practitioners. The polemic argument was too adversarial to make much progress towards promoting systematic review.

Fox describes more “conciliatory”<sup>1</sup> language employed by other proponents of systematic review. Rather than the abrupt, condescending tone described above, this second group begins with recognition of a problem, and confidence in the community to address it:

They emphasized the variation resulting from clinicians’ “collective uncertainty” about the “effectiveness and safety of many of the elements of care.” They apparently thought it politic to introduce the volumes with the reassuring assumption that as men and women of science, clinicians would reduce this variation when persuasive evidence of effectiveness became available.<sup>1</sup>

This “persuasive evidence” consisted of the systematic analysis that followed. Utilizing this second, more conciliatory approach helped encourage the adoption of systematic review in modern medicine.

#### *6.1.2 Discussion of administrative elements*

One of the major challenges in any animal compliance program is administrative burden. In April 2017, members of The Federation of American Societies for Experimental Biology (FASEB), the Association of American Medical Colleges (AAMC), the Council on Governmental Relations (COGR), and the National Association for Biomedical Research (NABR) met to discuss “actionable recommendations for promoting regulatory efficiency, animal welfare, and sound science.”<sup>1</sup> The primary focus of the workshop was administrative

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<sup>1</sup> FASEB, “Reforming Animal Research Regulations: Workshop Recommendations to Reduce Regulatory Burden,” 9.

burden. In this context administrative burden is defined as those activities which require excessive efforts, without providing any benefit to the compliance program, or assuring the wellbeing of animal subjects. Of particular interest in the workshop discussion was the “requirement” to conduct a literature search for alternatives to animals. As FASEB and colleagues point out, federal guidance on this issue is inconsistent. The Animal Welfare Act requires that the principal investigator “has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animals, and has provided a written narrative description of the methods and sources, *e.g.*, the Animal Welfare Information Center, used to determine that alternatives were not available.” The Act only requires that the IACUC provide “assurances demonstrating that the principal investigator considered alternatives to those procedures.”<sup>1</sup> However, USDA’s companion Animal Care Policy Manual recommends “a database search as the most effective and efficient method for demonstrating compliance with the requirement to consider alternatives to painful/distressful procedures.”<sup>2</sup> Similarly, PHS policy requires that an animal protocol in any funded research proposal must state the “rationale for involving animals, and for the appropriateness of the species and numbers used.” However, they do not specifically require a “literature search” in their policy, and incorporate the AWA by reference.<sup>3</sup> Therefore, FASEB and colleagues have recommended amending the USDA Animal

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<sup>1</sup> 89-544, P.L. *The Animal Welfare Act (Laboratory Animal Welfare Act of 1966, P.L. 89-544)*. 1966.

<sup>2</sup> *Animal Care Policy Manual (May 23, 2016) Currently under Revision*, by USDA APHIS, United States Department of Agriculture and USDA APHIS Animal and Plant Health Inspection Service, 2016.

<sup>3</sup> OLAW, Office of Laboratory Animal Welfare, *Public Health Service Policy on Humane Care and Use of Laboratory Animals*, 3.

Care Policy Manual “with respect to literature searches.”<sup>1</sup> This harmonization of federal policy would leave the requirement for a literature search up to each institution.

The Federal Demonstration Partnership (FDP), in collaboration with the National Academies, conducted a series of faculty workload surveys. The most recent survey, conducted in 2012, echoed some of the administrative concerns of the FASEB:

Animal care and use is the single most intensive of all of the categories of administrative responsibility associated with federally funded research.

The vast majority of those who work with animal subjects reported that meeting IACUC requirements took substantial time away from their ability to actively conduct research.

Respondents working with vertebrate animals cited “Preparing IACUC protocols for initial review” as the most time consuming activity. Although literature review was not specifically cited, respondents felt that “required protocols are unnecessarily lengthy.” Also cited were “inconsistencies in agency & institution requirements.”<sup>2</sup>

Additionally, Carlijn R. Hooijmans and colleagues at Radboud University Medical Centre point out that not all vertebrate animal research is applied or translational. Blanket institutional policies requiring systematic review for basic, fundamental vertebrate research may be unnecessary.<sup>3</sup>

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<sup>1</sup> FASEB, AAMC, COGR, and NABR. “Reforming Animal Research Regulation,” 26.

<sup>2</sup> Schneider, Sandra L. *2012 FDP Faculty Workload Survey: Research Report*. Commissioned by the Federal Demonstration Partnership. 2014.  
[https://sites.nationalacademies.org/cs/groups/pgasite/documents/webpage/pga\\_087667.pdf](https://sites.nationalacademies.org/cs/groups/pgasite/documents/webpage/pga_087667.pdf)

<sup>3</sup> Hooijmans, “Meta-Analyses of Animal Studies: An Introduction of a Valuable Instrument to Further Improve Healthcare,” 5.

Increasing administrative burden has the potential to open an institution up to risk of non-compliance or even serious misconduct. Authors J.R. Haywood and Molly Greene caution institutions against an “overzealous” approach, for risk of causing more harm than good to the institutional animal program. They categorize administrative burden into three types, 1.) legally mandated; 2.) “interpretation” of the law by federal agencies; and 3.) “self-imposed” burden resulting from institutional policies and procedures.<sup>1</sup> Introducing systematic review to an institutional animal program has the potential to fall into the latter category. Haywood and Greene cite many of the opportunities for scientific misconduct in such an environment, including “alienation of scientists and attempts to avoid compliance.” They also cite “difficulty in recruiting new scientists,” which is critical to the academic excellence of any institution.

Finally, they express concern for an adversarial academic/institutional relationship stating that “the amount of time it takes for research staff to complete compliance paperwork, serve on compliance committees, and participate in compliance training further exacerbates the problem.”<sup>2</sup>

Conducting a systematic review is undeniably time consuming. This is especially true for specialists, who already have extraordinary demands on their time. Fox and Bero have cited that medical institutions are not actively engaging in the recruitment of researchers who perform systematic review as a discipline.<sup>3</sup> Others, such as Michael Festing and Timo Nevalainen suggest

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<sup>1</sup> Haywood, JR. and Molly Greene. "Avoiding an Overzealous Approach: A Perspective on Regulatory Burden." *ILAR J* 49, no. 4 (2008): 426-34.

<sup>2</sup> Haywood, "Avoiding an Overzealous Approach: A Perspective on Regulatory Burden," 28.

<sup>3</sup> Fox, Daniel M. and Lisa Bero. "Systematic Reviews: Perhaps "the Answer to Policy Makers' Prayers"?" *Environmental Health Perspectives* 122, no. 10 (2014): A262-A63. <http://dx.doi.org/10.1289/ehp.1408599>

teaming up with statisticians in systematic review is a mutually beneficial collaboration.<sup>1</sup> The lack of faculty specializing in this type of analysis is recognized as both an administrative and cultural barrier to promoting the practice of systematic review.

### *6.1.3 Discussion of training elements*

There is a documented unease and distrust faculty have for any form of training. Often veiled as "faculty development," some forms of training, albeit necessary, are interpreted as an intellectual affront. Catherine Haras, Senior Director at the Center for Effective Teaching and Learning, at California State asks the question: "how do professionals continue to learn?"<sup>2</sup> This is especially challenging in those areas where training is not a requirement. Haras notes that research faculty are "experts," not generalists. As such, they tend to be self-directed in their learning activities. Advising faculty on what they "should" be learning is not the best approach. Also cited are ineffective venues for faculty development. Haras feels that lectures and workshops are problematic:

A lot of [Professional Development] can mirror teaching, devoted to content, not practice—to what is taught, and not how it is taught. [Professional Development] often relies on the workshop model, demonstrated to be ineffective. The implication is that knowledge about teaching and learning can be acquired through transfer and is primarily cognitive.<sup>3</sup>

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<sup>1</sup> Festing, Michael F. W. and Timo Nevalainen. "The Design and Statistical Analysis of Animal Experiments: Introduction to This Issue." *ILAR Journal* 55, no. 3 (2014): 379-82. <http://dx.doi.org/10.1093/ilar/ilu046>

<sup>2</sup> Haras, Catherine. "Faculty Development as an Authentic Professional Practice." *Higher Education Today* (2018). <https://www.higheredtoday.org/2018/01/17/faculty-development-authentic-professional-practice/>

<sup>3</sup> Haras, "Faculty Development as an Authentic Professional Practice," 30.



Therefore, Haras promotes a less cerebral, and more active, hands-on approach to faculty development. One in which training activity is virtually indistinguishable from professional activity. Additionally, non-tenure track and adjunct scientists are often overlooked, creating a gap in faculty development strategies. "As the faculty ranks become more diverse in terms of appointment types, faculty development should ensure that each faculty member, regardless of appointment type, feels supported."<sup>1</sup> Also of concern is the junior researcher. The graduate student is particularly vulnerable. A graduate student relies heavily on the faculty advisor, and not the institution, for guidance and training. If the faculty member is not effectively demonstrating best practice, it cannot be expected that the graduate student will employ best practices moving forward.

A significant challenge to creating an effective training program is the lack of understanding about training forums themselves. Particularly problematic is the "workshop" method. Although widely employed by institutions, it has proven ineffective at developing faculty. Many institutions employ a confused mix of *ad hoc* online and in-person platforms in usually short bursts (less than 24 hours of training time). In her book entitled "Authentic Professional Learning," Ann Webster-Wright refers to such professional development activities as "episodic information updates "delivered" to "deficient" professionals in a didactic manner."<sup>2</sup>

When such activities are institutionally mandated, they are easily dismissible as "administrative burden." Attendance is the minimum requirement for documenting compliance.

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<sup>1</sup> Sorcinelli, Mary Deane "Faculty Development: The Challenge Going Forward." *Peer Review, Association of American Colleges & Universities* 9, no. 4 (2007). <https://www.aacu.org/publications-research/periodicals/faculty-development-challenge-going-forward>

<sup>2</sup> Webster-Wright, Ann. *Authentic Professional Learning: Making a Difference through Learning at Work*. Vol. 2. Professional and Practice-Based Learning: Springer, 2010.

With the ease of electronic distractions such as smartphone access and an abundance of email, lack of attention in workshops is apparent. Similarly, most workshops are facilitated, meaning that they are conducted more like traditional lectures, and are not as participatory as they appear.

As an alternative, Webster-Wright promotes the practice of "authentic" training, which she describes as those programs that allow the participant to learn through practice within their professional environment, such as the laboratory. This approach recognizes the researcher's preference for self-guided learning, but still maintains a collaborative institutional culture. Her work promotes "realistic strategies for enhancing support for professionals to continue learning in ways that make sense to them as individuals, whilst contributing to an enhancement of their shared practice."<sup>1</sup>

A 2013 survey of the National Pediatric Residency program in Saudi Arabia found that a majority of respondents believed that research training would improve their practice, enhance their careers, and the care of their patients (89.2%). This demonstrates potential buy-in on behalf of faculty. However, over half of the respondents also admitted that training detracts from their discipline, hindering them from becoming an "expert in their field."<sup>2</sup> Promotion of an "authentic" training approach helps to integrate training and practice as one continuous, sustainable activity. Rather than a distraction, such integration makes training a core part of the research activity itself.

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<sup>1</sup> Webster-Wright, *Authentic Professional Learning: Making a Difference through Learning at Work*, 30.

<sup>2</sup> Alhaider, S. A., H. A. Alshehri, and S. A. Almedhesh. "Research Training, Productivity and Challenges among Trainees of Pediatric Residency Programs across Saudi Arabia." *International Journal of Pediatrics and Adolescent Medicine* 2, no. 2 (2015/06/01/ 2015): 70-74. <http://dx.doi.org/https://doi.org/10.1016/j.ijpam.2015.06.005>

To achieve this aim, Catherine Haras supports a "scaffolding" approach to training. This approach creates an "authentic" learning environment from the ground up, using an intellectually nurturing environment made up of faculty cohorts, informal mentoring opportunities, observation, evaluation, and feedback programs.<sup>1</sup> This is a long-term approach, requiring time and effort before the program reaches fruition.

Haras cites a handful of institutions employing a "scaffolded" technique. Among them is the Clinical Teaching Program at Stanford Medicine. The goals of the program are to "enhance participants' versatility as teachers," "enhance their ability to analyze clinical teaching using an educational framework," and "provide a forum for collegial exchange:"

The seminars consist of didactic presentations, group discussions, role-play exercises, video vignette review, and personal and institutional goal setting. During a follow-up session [sic], participants are encouraged to develop a set of recommendations for improving their institution's environment for clinical teaching.<sup>2</sup>

It should be noted that the goal of Stanford's program is to train teachers in a way that helps them train in a clinical setting. Stanford's teaching model provides an excellent framework that could be adapted to increase the practice of systematic review and meta-analyses.

#### *6.1.4 Review of policy elements*

Policy makers are increasingly interested in the results of comprehensive systematic review when making health policy decisions. Prior to the practice of systematic review, most

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<sup>1</sup> Haras, "Faculty Development as an Authentic Professional Practice," 29.

<sup>2</sup> Stanford Medicine, Stanford. "Clinical Teaching Program." Last modified 2018 (accessed 2018). [http://sfdc.stanford.edu/clinical\\_teaching.html](http://sfdc.stanford.edu/clinical_teaching.html)

policy decisions were made based on evidence presented by aggressive lobbyist or pharmaceutical firms, supported by a few single studies with desirable results. However, lawmakers in the United States increasingly seek out systematic analyses to inform healthcare decisions. With increased electronic access to systematic analyses, policy makers are making more informed decisions when it comes to healthcare, drugs, and interventions. For example, the Centers for Medicare and Medicaid Services began commissioning systematic reviews to inform their policy decisions as early as 1999.<sup>1</sup>

Many state regulations now require that systematic review inform policy determinations. The state of Wyoming recently made the Cochrane library free and available to all citizens.<sup>2</sup> The Canadian government has followed suit, pursuing publically available Cochrane licenses.<sup>3</sup>

However, unique political challenges exist. These challenges include short election cycles and countermeasures by pharmaceutical companies through advertising and news venues. Also, problematic is pushback from health care systems that rely on reimbursement for the very interventions that systematic evidence demonstrates as ineffective.<sup>4</sup>

Daniel Fox cites that The National Institutes of Health are increasingly embracing systematic review but provide few opportunities to develop the necessary tools. He cites the lack

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<sup>1</sup> Fox, Daniel. M. "Evidence of Evidence-Based Health Policy: The Politics of Systematic Reviews in Coverage Decisions." *Health Aff (Millwood)* 24, no. 1 (Jan-Feb 2005): 114-22. <http://dx.doi.org/10.1377/hlthaff.24.1.114>

<sup>2</sup> Libraries, University of Wyoming. "Advanced Pharmacy Experience Orientation: Publicly Available Databases." Last modified 2018. Accessed 2018. <https://uwyo.libguides.com/c.php?g=97804&p=632343>

<sup>3</sup> Mackay, Brad. "Cochrane Library to Be Available to All Canadians." *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 176, no. 7 (2007): 917-18. <http://dx.doi.org/10.1503/cmaj.070295>

<sup>4</sup> Fox, "Evidence of Evidence-Based Health Policy: The Politics of Systematic Reviews in Coverage Decisions," 33.

of overall funding and competing priorities for this shortfall.<sup>1</sup> This is troublesome given the increased need for what he terms “evidence based” research:

Members of the international Steering Group of the Cochrane Collaboration estimated in 2003 that about 10,000 reviews would be required to assess the current array of health care interventions. Unanticipated advances in laboratory and clinical research are likely to increase that estimate.<sup>2</sup>

The NIH provides many online resources for undertaking and understanding systematic review activities, including a fee-for-service model to assist the NIH community with systematic review.<sup>3</sup> Although funding for the systematic review of results sets within specific disciplines is more common, more funding for the promotion of systematic review and the improvement of overall tools is needed. However, there is growing interest in developing such tools. One recent example is an NIH award made to Neil Smalheiser and colleagues at the University of Illinois at Chicago. The project, entitled "Text Mining Pipeline to Accelerate Systematic Reviews in Evidence-Based Medicine" aims to integrate a computational tool that will improve the overall practice of systematic review.<sup>4</sup>

In addition to the need for increased systematic review, there is a need to provide policymakers with information that is easy to interpret by the layperson. Recently, in the field of

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<sup>1</sup> Fox, "Evidence of Evidence-Based Health Policy: The Politics of Systematic Reviews in Coverage Decisions," 33.

<sup>2</sup> Fox, "Evidence of Evidence-Based Health Policy: The Politics of Systematic Reviews in Coverage Decisions," 33.

<sup>3</sup> NIH, National Institutes of Health Office of Management. "Systematic Review Service." Last modified 2018 (accessed 2018). <https://www.nihlibrary.nih.gov/services/systematic-review-service>

<sup>4</sup> Smalheiser, Neil R., and Aaron M Cohen. "Text Mining Pipeline to Accelerate Systematic Reviews in Evidence-Based Medicine." *HHS/National Library of Medicine (NLM) Award No. 5R01LM010817-06* (2017). [https://projectreporter.nih.gov/project\\_info\\_details.cfm?aid=9310440](https://projectreporter.nih.gov/project_info_details.cfm?aid=9310440)

psychology, Cara Lewis and colleagues have begun a coordinated effort to assist with this dilemma by creating a review repository to improve the "interpretability, comparability, and generalizability." of systematic results sets.<sup>1</sup>

In a 2016 report entitled "Enhancing Research Reproducibility," the FASEB made recommendations for improving biological inquiry. Recommendations for improvement include the standardization of terms across agencies and institutes. FASEB also promotes the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines for common use in the biomedical community.<sup>2</sup>

One way in which universities can increase this type of support, is through increased engagement with policymakers. The National Co-coordinating Centre for Public Engagement in the United Kingdom (NCCPE) promotes what they term as an "engaged" technique. They cite that an engaged university is one that is "actively involving the public in the research activity of the institution," developing teaching activities with community impact, and maximizing those social benefits that the university can provide. Engaged universities also increase transparency and the flow of information to the public about their beneficial impact.<sup>3</sup>

If the benefits of systematic review are shown to have positive effects on public health and health policy, this will increase public support for these activities.

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<sup>1</sup> Lewis, Cara C., Kayne D. Mettert, Caitlin N. Dorsey, Ruben G. Martinez, Bryan J. Weiner, Elspeth Nolen, Cameo Stanick, Heather Halko, and Byron J. Powell. "An Updated Protocol for a Systematic Review of Implementation-Related Measures." *Systematic Reviews* 7, no. 1 (2018): 66. <http://dx.doi.org/10.1186/s13643-018-0728-3>

<sup>2</sup> FASEB Federation of American Societies for Experimental Biology, FASEB. *Enhancing Research Reproducibility: Recommendations from the Federation of American Societies for Experimental Biology* 2016. [http://faseb.org/Portals/2/PDFs/opa/2016/FASEB\\_Enhancing%20Research%20Reproducibility.pdf](http://faseb.org/Portals/2/PDFs/opa/2016/FASEB_Enhancing%20Research%20Reproducibility.pdf)

<sup>3</sup> NCCPE, National Coordinating Centre for Public Engagement. "What Does an Engaged University Look Like?" *About engagement* (2018). <http://www.publicengagement.ac.uk/about-engagement/what-does-engaged-university-look>

## 6.2 Summary of findings

This research examines four spheres of influence within an institution: cultural, administrative, training, and public policy. These areas have been identified because of significant overlap and their relevance to any institutional compliance program. However, it is noted that intersecting areas of influence can be problematic. There is a demonstrated conflict between academic freedom, public policy, and institutional administration. Faculty feedback provides evidence that animal compliance activity detracts from scientific research. However, faculty also demonstrate a willingness to learn practices that are more effective. This is especially true of practices that might improve their scientific standing. However, conflict arises in the form of perceived or actual administrative burden, flawed professional development models, and poor public engagement.

This research demonstrates examples of effective means of eliminating conflict within each intersecting sphere. Fox and colleagues demonstrate both effective and ineffective means of communicating within the scientific community. Haras and colleagues promote effective models that allow an institution to integrate training with daily experimental practice. The NCCPE demonstrates implementation of “engagement” technique, by citing the characteristics of institutions with successful public engagement practices.

The results of this research inform recommendations for institutions, so that they might create a culture of systematic review within their animal program. These recommendations will lead to the ultimate widespread adoption of systematic review as common practice in preclinical animal trials. These recommendations will improve scientific practice and institutional culture, and will ultimately reduce waste of institutional resources as well as the overall number of animal subjects themselves.

## Chapter 7. Recommendations

### 7.1. Introduction

The biomedical community is actively engaged in improving methods for comprehensive systematic review. Systematic review activities allow for a comprehensive comparison of the results of many experiments. Historically, systematic review in the medical community has proven that some common practices are ineffective or even harmful. Initially, there was resistance from practitioners and policymakers. However, increased systematic review has aided the medical community in promoting only the most promising interventions for clinical trial. Many clinical trials begin with preclinical studies in vertebrate animals. This is known as *translational* research. The notable lack of systematic review in preclinical animal trials leads to many challenges. These include repetition of protocols that have been already proven ineffective, and commencing clinical trials in human subjects on potentially harmful interventions. Benefits of systematic review also include the potential to increase reproducible results thus reducing the number of animals used in research-overall.

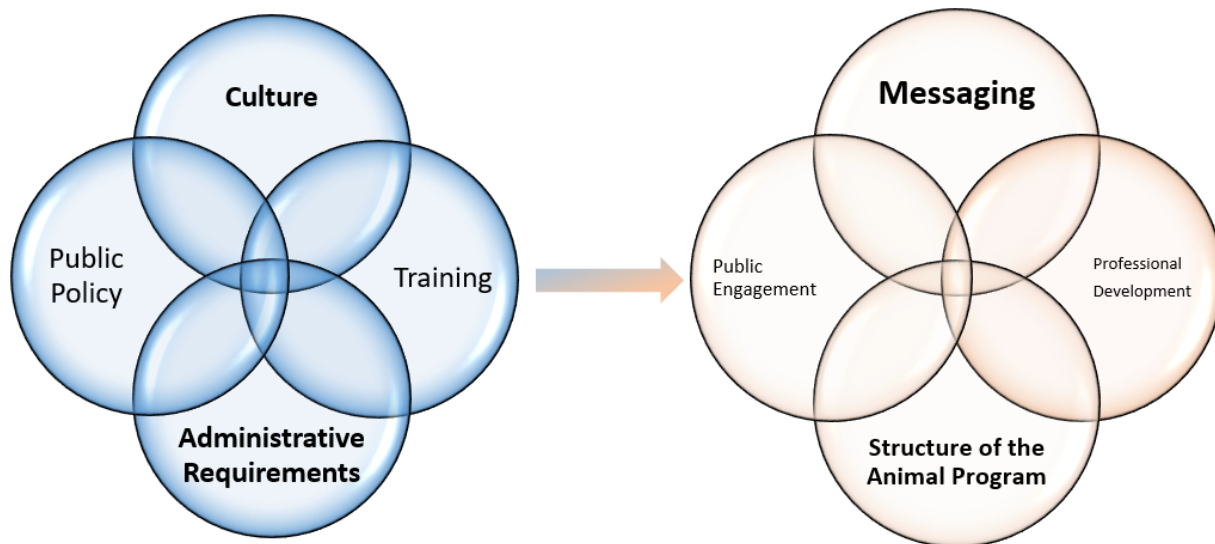
Institutions of higher education have an opportunity to promote systematic review as a best practice in the development of animal protocols. However, concerns of academic freedom and administrative burden must first be addressed.

This report demonstrates four areas where an institution can promote the practice of systematic review. Institutional culture, administration, training, and policy engagement are discussed. These four spheres of influence provide an opportunity for scientific excellence. Recommendations are made which enhance each sphere of influence, to improve the animal program, and increase the practice of systematic review.

### 7.2. Recommendations and Discussion



Animal compliance programs at universities and research institutes are well positioned to support increased systematic review activity. However, an institution must avoid implementing any sort of “hard line” requirement for systematic review. Such efforts have the potential to create undue administrative burden and sour the relationship between academics and administration. Instead, a four-fold approach is recommended that promotes a culture of systematic review. This approach focuses on four critical elements that, when implemented in concert, serve to increase the instance of systematic review in the vertebrate research community, and promote scientific excellence. These areas are administrative, cultural, public policy, and training-related. They can be easily translated by an institution through actionable means by restructuring the institutional animal program, institutional messaging, faculty and staff development, and strategic public engagement:



**Figure 1.2.** Four spheres of institutional influence easily translate into means for actionable improvement.

### *7.2.1 Recommendations for institutional messaging*

Institutional messaging has great potential to establish a collaborative research environment. Mark Frankel of the American Association for the Advancement of Science eloquently describes the driver for messaging within an institution:

A profession's code of ethics is perhaps its most visible and explicit enunciation of its professional norms. A code embodies the collective conscience of a profession and is testimony to the group's recognition of its moral dimension.<sup>1</sup>

Therefore, an institution must routinely revisit its mission and vision. A large research institution will have many distinct operations, each with their own unique, sometimes contradictory, vision. An alignment and harmonization of vision statements from the top-most university leadership to the animal compliance program is required. As demonstrated by Daniel Fox, the language used to convey institutional intent is critical.<sup>2</sup>

Aurora Brønstad and Anne-Grethe Trønsdal Berg suggest language to alleviate the perception of administrative burden. For example, they cite university strategies that employ the term "adherence" or "concordance" in place of "compliance."

For many people, 'compliance' implies a paternalistic relationship, in which one party has the superior role and orders the subordinate party to use the 'right' solutions.<sup>3</sup>

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<sup>1</sup> Frankel, Mark S. "Professional Codes: Why, How, and with What Impact?" *Journal of Business Ethics* 8, no. 2-3 (1989): 109-15. <https://doi.org/10.1007/BF00382575>

<sup>2</sup> Fox, "Systematic Reviews and Health Policy: The Influence of a Project on Perinatal Care since 1988," 24.

<sup>3</sup> Brønstad, Aurora. and Anne-Grethe Berg. "The Role of Organizational Culture in Compliance with the Principles of the 3rs." *Lab Anim (NY)* 40, no. 1 (Jan 2011): 22-6. <http://dx.doi.org/10.1038/labani0111-22>.

As noted previously, this "paternalistic" approach is not well received by faculty. Andrew Jefcoat of the University of Wisconsin-Madison cites the three most common reasons for non-compliance with an animal program. They are "lack of information," "desperation," and "disregard."<sup>1</sup> One of the best ways to avoid fostering such attitudes is to strategically implement the messaging used by the IACUC. Collaborative language is recommended to convey not only good intention, but also to set the tone, so that all members of the institution have "buy-in."

Another tool to promote systematic review is in the publication of institutional "position statements." Like mission statements, position statements help set the institutional tone. They are generally timely, in response to a relevant topic, and publically disseminated.

The American College of Laboratory Animal Medicine (ACLAM) demonstrates an effective process for drafting an institutional position statement.<sup>2</sup> Based on their model, best practices include:

- Recruiting a committee of volunteers from both faculty and staff charged with drafting the initial statement
- Identifying a spokesperson(s). Ideally a shared appointment between the RIO and the Attending Veterinarian.
- Ensuring that the animal program statement is aligned with the larger university mission statement
- Widely disseminating the draft to all members of the institution for comment

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<sup>1</sup> Jefcoat, Andrew M. "The 'Triad of Noncompliance' as a Tool for Understanding, Preventing and Correcting Protocol and Procedural Noncompliance." *Lab Anim. (NY)* 37 (// 2008): 459-63.

<sup>2</sup> ACLAM, The American College of Laboratory Animal Medicine. "Overview for Development of ACLAM Position Papers /Statements." (accessed 2018). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5113890/>

- Thoughtfully and intentionally responding to feedback from the comment period in subsequent drafts
- Publicizing the final statement of position in academic journals, campus communications, and media venues
- Acknowledging the contributions of the research faculty and staff in the final outcome

Position statements can have significant impact. For example, the ACLAM position statement on “Reproducibility” emphasizes the importance of Systematic Review:

Although characterized by observation and experimentation, advances in science greatly depend upon peer-based communication and evaluation to ensure that new information is analyzed, verified, and confirmed. Ideally, published studies should include methodological and procedural descriptions, environmental conditions and meta-information, which should be readily accessible and provided in sufficient detail to enable a knowledgeable and capable researcher to replicate experiments and achieve equivalent results.<sup>1</sup>

Once the need is identified, the body of the ACLAM statement establishes some institutional norms, such as use of the ARRIVE guidelines. The ACLAM concludes this position statement by recognizing the collaborative efforts that will be required to address this need:

In conclusion, it is incumbent on laboratory animal veterinarians and the scientific community to define elements of study design that affect experimental reproducibility. Scientific progress relies on rigor and

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<sup>1</sup> ACLAM, "Overview for Development of ACLAM Position Papers /Statements," 40.

reproducibility, particularly for advances made possible by comparative medical research with animals.<sup>1</sup>

Ernest D. Prentice, of the University of Nebraska Medical Center writes extensively on the role and function of an IACUC. He has been heavily involved in both human and animal compliance programs over the course of his career, having recently been appointed to the Association of Clinical Research Professionals (ACRP) Board of Trustees.<sup>2</sup> Prentice recommends designing a dynamic and collaborative IACUC environment. This is in contrast to the traditional chair/member model, and instead encourages open dialogue and equal footing among all members of the committee. Prentice believes in improving institutional culture as a means of setting the stage for an effective IACUC. He recommends widely disseminated and highly visible mission statements. Also recommended are "attestation statements" to be signed by faculty and staff:

The mission statement should be directly disseminated to all employees, and also be posted in laboratories and animal care facilities where personnel can receive daily reminders of their obligations. Indeed, a compelling case can be made for requiring all researchers and animal care personnel to sign their understanding.<sup>3</sup>

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<sup>1</sup> ACLAM, "Overview for Development of ACLAM Position Papers /Statements," 40.

<sup>2</sup> Spellman, Lisa. "UNMC's Ernest Prentice, Ph.D., Named to National Clinical Research Board." *University of Nebraska Newsroom* (December 19, 2016 2016). <https://www.unmc.edu/news.cfm?match=19766>.

<sup>3</sup> Prentice, Ernest D., M. Elizabeth Blackburn, and Robert S. Dixon. "Fostering Collaborative Roles and Responsibilities for Members of an IACUC or Oversight Body." In *Management of Animal Care and Use Programs in Research, Education, and Testing*, edited by nd, R. H. Weichbrod, G. A. H. Thompson, and J. N. Norton, 27-34. Boca Raton (FL): CRC Press/Taylor & Francis (c) 2018 by Taylor & Francis Group, LLC., 2018.

Passively posting mission statements on the internet, or disseminating them via email does not have the same impact on campus culture as the more visible, participatory methods recommended above.

### *7.2.2 Recommendations for administrative structure*

Faculty feel that IACUCs can be administratively burdensome, overstepping their responsibility by critiquing experimental design.<sup>1</sup> However, the IACUC has a unique opportunity to engage faculty by alleviating burden and promoting best practice.

The IACUC is one body within a larger compliance program often referred to as the "Animal Program." The Guide requires that the program be governed by three primary entities, The IACUC, The Attending Veterinarian, and the Institutional Official. However, there is some measure of flexibility in staffing the larger Animal Program.

Haywood, Greene, Jefcoat, and others have previously cited compliance risk with administratively burdensome IACUC processes.<sup>2</sup> Jefcoat recommends three ways in which the IACUC can dispel any misconceptions about their intent using "education," "assistance," and "anxiety reduction."<sup>3</sup> Recommended activities include positioning the IACUC as a resource, not a gatekeeper. Examples include:

- Advertising to faculty that assistance is available to them, especially in times of need, such as tight turn-around

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<sup>1</sup> FASEB, "Reforming Animal Research Regulations: Workshop Recommendations to Reduce Regulatory Burden," 9.

Levin, "Response to Protocol Review: Help IACUC Understand the Science," 23.

<sup>2</sup> Haywood, "Avoiding an Overzealous Approach: A Perspective on Regulatory Burden," 28.

<sup>3</sup> Jefcoat, "The 'Triad of Noncompliance' as a Tool for Understanding, Preventing and Correcting Protocol and Procedural Noncompliance." 39.

- Recognizing the scientific accomplishments of the researcher, and inviting their opinion
- Collaborating with faculty on solutions to challenges
- Reminding faculty that one of the goals of the IACUC is to alleviate burden
- Soliciting regular feedback from faculty in an effort to improve processes and messaging

Meeting these goals does require investment on behalf of the institution. A support structure should be built to assist the IACUC. Prentice recommends staffing an animal program office with an Administrative Manager. This individual should be a professional, knowledgeable in animal compliance and regulation. Their role should not be confined to that of a committee coordinator or administrative assistant. Administrative activities should include design and implementation of training programs and coordination of messaging. In addition to professional excellence in the area of animal compliance, Prentice recommends recruiting someone with the soft skills required to navigate a diverse group of stakeholders:

The most important characteristics for an IACUC administrator to possess are analytical thinking skills, organizational ability, written and verbal communication proficiency, and personality traits that allow him or her to work diplomatically with strong-willed, and sometimes difficult, researchers and committee members.<sup>1</sup>

Other recommendations for improving IACUC functionality include streamlining the IACUC review process. Andrea Liberale and Jamison Kovach of the University of Houston suggest two approaches that have been successful in streamlining the Institutional Review Board (IRB) for human subjects research. Firstly, they promote an evaluation of IRB discourse to examine what ethical issues or concerns tend to dominate (or stagnate) the protocol discussion.

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<sup>1</sup> Prentice, "Fostering Collaborative Roles and Responsibilities for Members of an IACUC or Oversight Body," 42.

Secondly, they suggest increasing the number of IRB committees, and reducing meeting times into smaller, more manageable increments:

This approach not only reduced the time to obtain IRB approval/denial decisions by nearly 50 percent, but it also increased the quality of reviews because more frequent meetings with shorter agendas allowed committee members to more carefully review each protocol.<sup>1</sup>

Other recommendations include:

- Accommodating meetings between members of the committee and faculty before protocol development is complete.
- Inviting objective outside experts on a case-specific basis, in an effort to bring a highly specialized subject-matter expert into the protocol review process.
- Providing uniform template protocols that include desirable elements, such as systematic review checklists.
- Eliminating review of irrelevant elements, on a case-specific basis.

These recommendations are easily adaptable and will help to improve the functionality of the IACUC.

### *7.2.3 Recommendations for professional development*

As previously discussed, traditional training programs are both unpopular and ineffective. Catherine Haras Senior Director at the Center for Effective Teaching and Learning at California

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<sup>1</sup> Pescina Liberale, Andrea and Jamison V. Kovach. "Reducing the Time for IRB Reviews: A Case Study." *Journal of Research Administration* 48, no. 2 (2017): 37-50.  
[http://download.srainternational.org/journal/archive/JRA\\_V48n2-2017.pdf](http://download.srainternational.org/journal/archive/JRA_V48n2-2017.pdf).



State, suggests development of a "scaffolded" training program. She outlines common traits shared by successful programs, which can be condensed into five critical elements:<sup>1</sup>

- Training modules avoid the “workshop” forum whenever practicable. Instead they are "experiential, and avoid lecturing."
- They "set an expectation of practice for participants."
- They are longitudinal, and "include follow up after programming has finished."
- They provide an opportunity for researchers to coach and mentor each other.
- Training occurs "in the workplace, where faculty are, and where they struggle."

Institutions should develop a program that introduces the practice of systematic review in a real-world research setting. Further recommendations include:

- Pairing statisticians with faculty to address specific statistical needs.
- Recruiting and retaining faculty with technical expertise in conducting systematic review.
- Recognizing systematic review as a scientific discipline, and not just a service of the library.
- Providing access to systematic review tools and databases for self-directed exploration within the lab as opposed to off-site software demonstrations.
- Providing internal funding opportunities for graduate students in the advancement of systematic review tools and activities.
- Investing in match funds for systematic review that compliments federally funded protocols.
- Provide evaluative peer-reviewed services for faculty interested in improving their skills.

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<sup>1</sup> Haras, "Faculty Development as an Authentic Professional Practice," 29.

- Evaluate the training program regularly, seek feedback from participating faculty, and be flexible enough to adjust, as needed.

Other recommendations include engaging faculty advisory groups to help ensure the educational framework is the best fit for the institution. The forum and methods of each institution will be unique; however, a program that incorporates these elements will find success in promoting systematic review.

#### *7.2.4 Recommendations for policy engagement*

Policy engagement is closely aligned with institutional messaging. The NCCPE promotes what they term as an "engaged" technique.<sup>1</sup> They cite that public engagement takes on many forms such as "citizen science," "outreach," and "social responsibility." All publically engaging universities have four common characteristics, which make them visible to policymakers:

- They actively "involve the public in the research activity of the institution."
- They promote teaching activities that directly affect the community and provide opportunities for students to interact with the community.
- They allow for transparent flow of information between the university and the public.
- They "maximize" opportunities to be socially responsible.

As previously discussed, governments increasingly commission systematic review to inform health policymaking. In an effort to promote systematic review in the animal sciences, further recommendations include:

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<sup>1</sup> NCCPE, "What Does an Engaged University Look Like?" 35.

- Highlighting the benefits of systematic review in promotion of the 3Rs. This might include public notices, letters to editors, or “social contracts” describing how systematic reviews reflect the institutional commitment to reduction, refinement, and replacement.
- Training policy makers to help them understand how to interpret systematic analyses.
- Publically acknowledging the contributions of scientists in the utilization of systematic review.
- Some jurisdictions have made databases, such as Cochrane, publically available. Consider augmenting these public efforts with an outreach program to assist the public in interpretation of results.
- Review the strategic plans of major funding agencies such as the National Institutes of Health. Publically demonstrate ways in which financial support for building the tools needed for systematic review aligns with the goals of the agency.

Participating in the activities recommended above will improve university-government relations and promote awareness of the benefits of systematic review both within and without your institution. Additionally, increased funding for systematic review and meta-analyses tools will help increase the overall number and quality of future reviews.

## Chapter 8: Conclusion

Systematic Review is defined as “research synthesis of multiple studies, enabling increased and efficient access to evidence.”<sup>1</sup> As evidenced by an overwhelming amount of support from the publishing community, systematic review and meta-analysis are commonly

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<sup>1</sup> Green, S. "Systematic Reviews and Meta-Analysis." *Singapore Med J* 46, no. 6 (Jun 2005): 270-3; quiz 74.

employed in medicine when drafting clinical trial protocol.<sup>1</sup> Because many clinical trials begin with preclinical experiments using vertebrate animals, there is a need for increased systematic review in the design of animal protocols.<sup>2</sup> Lack of such activity has the potential to have harmful downstream effects on the wellbeing of human participants. An example is the Food and Drug Administration's "Animal Rule," which allows for the marketing of substances not tested in a clinical setting.<sup>3</sup> Many also cite the lack of meta-analysis informing vertebrate study design as detrimental to the validity of research results, causing the promotion of otherwise ineffective treatments.<sup>4</sup> Systematic review and meta-analysis have the potential to improve the quality and reproducibility of vertebrate research protocols, resulting in more reliable results.<sup>5</sup>

The conduct of vertebrate research is governed by the Institutional Animal Care and use Committee (IACUC). However, the jurisdiction of the IACUC is largely that of regulatory compliance and literature search is generally not discussed in protocol review and approval sessions.<sup>6</sup> Furthermore, the IACUC can be perceived as administratively burdensome, and at odds with academic freedom.<sup>7</sup> However, notable organizations such as the International Council for Laboratory Animal Science (ICLAS) feel that poor scientific methods are "perpetuated by

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<sup>1</sup> PRISMA, "PRISMA Endorsers," 6.

<sup>2</sup> Hooijmans, "Progress in Using Systematic Reviews of Animal Studies to Improve Translational Research" 6.

<sup>3</sup> FDA, Food and Drug Administration. *Product Development under the Animal Rule, Guidance for Industry*, 6.

<sup>4</sup> Peters, "A Systematic Review of Systematic Reviews and Meta-Analyses of Animal Experiments with Guidelines for Reporting," 6.

<sup>5</sup> Hooijmans, "Meta-Analyses of Animal Studies: An Introduction of a Valuable Instrument to Further Improve Healthcare." 5.

<sup>6</sup> Silverman, "Decision Making and the IACUC: Part 1—Protocol Information Discussed at Full-Committee Reviews," 18.

<sup>7</sup> Prentice, "Scientific Merit Review: The Role of the IACUC," 10.

virtue of being previously published.” and that “sound” scientific results will further reduce the number of animals needed to advance biomedical research.<sup>1</sup>

This report identifies four areas of institutional influence: culture, administration, training, and public policy. Further examination of those areas where these spheres intersect has identified some problems, such as conflicting regulatory interpretation,<sup>2</sup> administrative burden,<sup>3</sup> and ineffective professional development programs.<sup>4</sup> However, this report also identifies effective solutions that have been utilized in related fields. Effective means of communicating the benefits of systematic review in the medical community provide an example.<sup>5</sup>

Institutional recommendations can be implemented within the institution to not only increase systematic review in preclinical animal trials, but also improve university function, culture, and public image. These recommendations allow an institution to implement a best practice while avoiding additional administrative or regulatory requirements. These recommendations are flexible enough to be tailored to each unique institutional atmosphere. Ultimately, widespread implementation of these practices will assist with the reduction of overall animal subjects and increased reliable interventions for human health.

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<sup>1</sup> ICLAS, "Guidelines for Researchers," 23.

<sup>2</sup> FASEB, "Reforming Animal Research Regulations: Workshop Recommendations to Reduce Regulatory Burden," 9.

<sup>3</sup> Schneider, "2012 Faculty Workload Survey," 28.

<sup>4</sup> Haras, "Faculty Development as an Authentic Professional Practice," 29.

<sup>5</sup> Fox, "Systematic Reviews and Health Policy: The Influence of a Project on Perinatal Care since 1988," 25.

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## Appendices

### *Brief Biography of the Author*

Elizabeth Estabrook is Associate Director of The Office of Sponsored Research at Cornell University's College of Agriculture and Life Sciences. The Office of Sponsored Research provides both administrative support and funding development strategies for a diverse group of faculty, spanning many disciplines, including biological statistics and animal sciences. Her interest in vertebrate animal research compliance stems from related activities in support of Cornell University's agricultural, translational, and veterinary research goals.

### *Key Words*

Animal Research Compliance, IACUC, Meta-Analysis, Systematic Review, Translational Research, Vertebrate research.